Précis

Metastatic breast cancer remains to this day a mostly incurable disease, with less than 10% of patients reaching a long-term disease free survival. Unfortunately, the more recently introduced strategy of high-dose chemotherapy and autologous transplantation is unlikely to achieve a high cure rate by itself. However, trends towards improvement in time to progression are seen, consistent with a greater reduction of tumor bulk. Our own experience in high-dose therapy and autologous progenitor cell transplantation for metastatic breast cancer (NCI protocol 96-C-0104) has allowed us to define two groups of patients, hormone receptor (HR) positive (i.e. ER or PR positive) and negative tumors, with very different event-free survival (EFS) following transplantation. This study proposes to treat patients with previously untreated metastatic breast cancer using the high-dose chemotherapy as a platform for immunotherapy. It is based on the following hypotheses and understanding:

- High-dose chemotherapy provides a platform for subsequent immunotherapy by:
  - Lengthening the progression-free survival period, thus allowing time for a slow acting therapy such as vaccination to be effective.
  - Maximally decreasing the patient's tumor burden. This has been shown both in clinical and experimental settings to be desirable if not necessary for immunotherapy to be effective.
  - Decreasing the tumor burden which may also decrease a tumor-induced immuno-suppressive effect linked to tumor bulk.
  - Providing tumor antigen exposure following transplantation in the form of repeated immunizations. This may take advantage of the pattern of immune reconstitution following high-dose chemotherapy at early time points (antigen-driven peripheral expansion of T-cells) and the renewal of a T-cell repertoire biased towards tumor antigens and anti-tumor responses at later time points.
- Low antigenicity of tumor antigens and immune tolerance may be overcome in a clinically relevant fashion by providing exposure to the tumor antigen (in our case, the carcino-embryonic antigen CEA) in a more immunogenic presentation along with added co-stimulatory signal (in the form of two poxvirus-based recombinant vaccines).
- Due to the post transplantation defects and delay in immune reconstitution, an adequate immune response to vaccines may not occur unless the patients are provided, following transplantation, with unaltered T-cells in the form of re-infusion of pre-chemotherapy lymphocytes.
- The late recovery of thymic function post transplantation (18 to 24 months) with reappearance of naïve T-cells may play a determinant role in the prevention of later disease progression. It is the rationale for a late series of immunizations.

Patients will receive conventional induction therapy with Paclitaxel, Cyclophosphamide and Doxorubicin, surgery and / or radiation as indicated for local control, then high-dose chemotherapy with Melphalan and Etoposide. Before any chemotherapy is started, patients will be immunized with one of two tumor-specific, recombinant, poxvirus-based DNA vaccines (r**V**-CEA(6D)/TRICOM) and lymphocytes will be cryopreserved. Following transplantation, patients will receive four series of immunization boosts (r**F**-CEA(6D)/Tricom) over the next 28 months. The primary objectives are to evaluate biologically this immunization strategy by assessing CEA-specific T-cell responses as well as clinically by comparing the patient EFS to our historical control (protocol 96-C-0104) in which patients have received the same conventional and high-dose therapy but no immunizations.